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| <input type="checkbox"/> | L15 | L14 and (IgE)adj(constant)adj(region) | 2 |
| <input type="checkbox"/> | L14 | L13 and IgE | 186 |
| <input type="checkbox"/> | L13 | L12 and Fc | 283 |
| <input type="checkbox"/> | L12 | L11 and allergy | 371 |
| <input type="checkbox"/> | L11 | (fusion)adj(molecule) | 1697 |
| <input type="checkbox"/> | L10 | (IgE)adj(CH2)adj(CH3)adj(CH4) | 4 |
| <input type="checkbox"/> | L9 | (IgE)adj(CH2)adj(CH3)adj(CH4)adj(Fc) | 0 |
| <input type="checkbox"/> | L8 | L2 and GE2 | 1 |
| <input type="checkbox"/> | L7 | L2 and (IgE)adj(heavy)adj(chain)adj(constant) | 1 |
| <input type="checkbox"/> | L6 | L2 and (IgG)adj(heavy)adj(chain)adj(constant) | 13 |
| <input type="checkbox"/> | L5 | L4 and Fc | 11 |
| <input type="checkbox"/> | L4 | L2 and (IgE)adj(Fc) | 11 |
| <input type="checkbox"/> | L3 | L2 and (IgE)adj(Fc)same(CH2-CH3-CH4) | 0 |
| <input type="checkbox"/> | L2 | (chimeric)adj(protein)same(fusion) | 5238 |
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=> s "Fce-Fcg"

L1 0 "FCE-FCG"

=> s "GE2"

L2 904 "GE2"

=> s l2 and Fc

L3 31 L2 AND FC

=> s l3 and fusion

L4 18 L3 AND FUSION

=> dup remove l4

PROCESSING COMPLETED FOR L4

L5 5 DUP REMOVE L4 (13 DUPLICATES REMOVED)

=> d l5 1-5 cbib abs

L5 ANSWER 1 OF 5 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 1

2004357862 EMBASE Co-aggregation of **Fc**.gamma.RII with **Fc**
εRI on human mast cells inhibits antigen-induced secretion and
involves SHIP-Grb2-Dok complexes. Kepley C.L.; Taghavi S.; Mackay G.; Zhu
D.; Morel P.A.; Zhang K.; Ryan J.J.; Satin L.S.; Zhang M.; Pandolfi P.P.;
Saxon A. C.L. Kepley, Dept. of Internal Medicine, Div. of Rheumatol.,
Allerg./Immunol., MCV Station, P. O. Box 263, Richmond, VA 23298, United
States. clkepley@mail1.vcu.edu. Journal of Biological Chemistry Vol. 279,
No. 34, pp. 35139-35149 20 Aug 2004.

Refs: 64.

ISSN: 0021-9258. CODEN: JBCHA3

Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 20040916

AB Signaling through the high affinity IgE receptor **Fc**.epsilon.RI
on human basophils and rodent mast cells is decreased by co-aggregating
these receptors to the low affinity IgG receptor **Fc**.gamma.RII.
We used a recently described **fusion** protein, **GE2**,
which is composed of key portions of the human γ1 and the human
ε heavy chains, to dissect the mechanisms that lead to human mast
cell and basophil inhibition through co-aggregation of **Fc**
γRII and **Fc**.epsilon.RI. Unstimulated human mast cells
derived from umbilical cord blood express the immunoreceptor
tyrosine-based inhibitory motif-containing receptor **Fc**.gamma.RII
but not **Fc**.gamma.RI or **Fc**.gamma.RIII. Interaction of

the mast cells with **GE2** alone did not cause degranulation. Co-aggregating **Fc.epsilon.RI** and **Fc.gamma.RII** with **GE2** 1) significantly inhibited IgE-mediated histamine release, cytokine production, and Ca(2+) mobilization, 2) reduced the antigen-induced morphological changes associated with mast cell degranulation, 3) reduced the tyrosine phosphorylation of several cellular substrates, and 4) increased the tyrosine phosphorylation of the adapter protein downstream of kinase 1 (p62(dok); Dok), growth factor receptor-bound protein 2 (Grb2), and SH2 domain containing inositol 5-phosphatase (SHIP). Tyrosine phosphorylation of Dok was associated with increased binding to Grb2. Surprisingly, in non-stimulated cells, there were complexes of phosphorylated SHIP-Grb2-Dok that were lost upon IgE receptor activation but retained under conditions of **Fc epsilon-Fc.gamma.** co-aggregation. Finally, studies using mast cells from Dok-1 knock-out mice showed that IgE alone triggers degranulation supporting an inhibitory role for Dok degranulation. Our results demonstrate how human **Fc.epsilon.RI**-mediated responses can be inhibited by co-aggregation with **Fc.gamma.RIIB** and implicate Dok, SHIP, and Grb2 as key intermediates in regulating antigen-induced mediator release.

L5 ANSWER 2 OF 5 MEDLINE on STN DUPLICATE 2
 2005032334. PubMed ID: 15640700. Genetically engineered negative signaling molecules in the immunomodulation of allergic diseases. Saxon Andrew; Zhu Daocheng; Zhang Ke; Allen Lisa Chan; Kepley Christopher L. (The Hart and Louise Lyon Laboratory, Division of Clinical Immunology/Allergy, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095-1680, USA.. asaxon@mednet.ucla.edu). Current opinion in allergy and clinical immunology, (2004 Dec) Vol. 4, No. 6, pp. 563-8. Ref: 29. Journal code: 100936359. ISSN: 1528-4050. Pub. country: United States. Language: English.

AB PURPOSE OF REVIEW: This review summarizes current knowledge regarding the control of human mast cell and basophil signaling and recent developments using a new therapeutic platform consisting of a human bifunctional gamma and epsilon heavy chain (**Fc gamma-Fc epsilon**) protein to inhibit allergic reactivity. RECENT FINDINGS: Crosslinking of **Fc gamma RIIB** to **Fc epsilon RI** on human mast cells and basophils by a genetically engineered **Fc gamma-Fc epsilon** protein (**GE2**) leads to the inhibition of mediator release upon **Fc epsilon RI** challenge. **GE2** protein was shown to inhibit cord blood-derived mast cell and peripheral blood basophil mediator release in vitro in a dose-dependent fashion, including inhibition of human IgE reactivity to cat. IgE-driven mediator release from lung tissue was also inhibited by **GE2**. The mechanism of inhibition in mast cells included alterations in IgE-mediated Ca mobilization, spleen tyrosine kinase phosphorylation and the formation of downstream of kinase-growth factor receptor-bound protein 2-SH2 domain-containing inositol 5-phosphatase (dok-grb2-SHIP) complexes. Proallergic effects of Langerhan's like dendritic cells and B-cell IgE switching were also inhibited by **GE2**. In vivo, **GE2** was shown to block passive cutaneous anaphylaxis driven by human IgE in mice expressing the human **Fc epsilon RI** and inhibit skin test reactivity to dust mite antigen in a dose-dependent manner in rhesus monkeys. SUMMARY: The balance between positive and negative signaling controls mast cell and basophil reactivity, which is critical in the expression of human allergic diseases. This approach using a human **Fc gamma-Fc epsilon fusion** protein to co-aggregate **Fc epsilon RI** with the **Fc gamma RII** holds promise as a new therapeutic platform for the immunomodulation of allergic diseases and potentially other mast cell/basophil-dependent disease states.

L5 ANSWER 3 OF 5 MEDLINE on STN DUPLICATE 3
 2004433011. PubMed ID: 15316510. Inhibition of allergen-specific IgE reactivity by a human Ig Fcgamma-Fcepsilon bifunctional **fusion**

protein. Zhang Ke; Kepley Christopher L; Terada Tetsuya; Zhu Daocheng; Perez Hector; Saxon Andrew. (Hart and Louis Lyon Laboratory, Division of Clinical Immunology and Allergy, Department of Medicine, University of California Los Angeles School of Medicine, CA 90095-1680, USA.) The Journal of allergy and clinical immunology, (2004 Aug) Vol. 114, No. 2, pp. 321-7. Journal code: 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB BACKGROUND: Coaggregating FcepsilonRI with FcgammaRII receptors holds great potential for treatment of IgE-mediated disease by inhibiting FcepsilonRI signaling. We have previously shown that an Fcgamma-Fcepsilon fusion protein, human IgG-IgE Fc fusion protein (GE2), could inhibit FcepsilonRI-mediated mediator releases in vitro and in vivo. OBJECTIVE: We sought to test whether GE2 was capable of blocking mediator release from FcepsilonRI cells sensitized with IgE in vivo or in vitro before exposure to GE2, a critical feature for GE2 to be clinically applicable. METHODS: GE2 was tested for its ability to inhibit Fel d 1-induced mediator release from human blood basophils from subjects with cat allergy, human lung-derived mast cells, human FcepsilonRIalpha transgenic mice sensitized with human cat allergic serum, and rhesus monkeys naturally allergic to the dust mite Dermatophagoides farinae. RESULTS: Basophils from subjects with cat allergy and lung mast cells degranulate when challenged with Fel d 1 and anti-IgE, respectively. GE2 itself did not induce mediator release but strongly blocked this Fel d 1- and anti-IgE-driven mediator release. GE2 was able to block Fel d 1-driven passive cutaneous anaphylaxis at skin sites sensitized with human serum from subjects with cat allergy in human FcepsilonRIalpha transgenic mice, but by itself, GE2 did not induce a passive cutaneous anaphylaxis reaction. Finally, GE2 markedly inhibited skin test reactivity to D farinae in monkeys naturally allergic to this allergen, with complete inhibition being observed at 125 ng. CONCLUSION: GE2 is able to successfully compete for FcepsilonRs and FcgammaRs on cells presensitized in vitro and in vivo and lead to inhibition of IgE-mediated reactivity through coaggregation of FcepsilonRI with FcgammaRII.

L5 ANSWER 4 OF 5 MEDLINE on STN DUPLICATE 4
2003414071. PubMed ID: 12801927. Inhibition of interleukin-4-induced class switch recombination by a human immunoglobulin Fc gamma-Fc epsilon chimeric protein. Yamada Takechiyo; Zhu Daocheng; Zhang Ke; Saxon Andrew. (Hart and Louis Laboratory, Division of Clinical Immunology, Department of Medicine, UCLA School of Medicine, California 90095-1680, USA.. ymdtkcy@fmsrsa.fukui-med.ac.jp) . The Journal of biological chemistry, (2003 Aug 29) Vol. 278, No. 35, pp. 32818-24. Electronic Publication: 2003-06-11. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Immunoglobulin E (IgE) is important in mediating human allergic diseases. We tested the hypothesis that a human Ig Fc gamma-Fc epsilon bifunctional chimeric protein, GE2, would inhibit IgE class switch recombination (CSR) by co-aggregating B-cell CD32 and CD23. Indeed, GE2 directly inhibited epsilon germ-line transcription, subsequent CSR to epsilon and IgE protein production. This CSR inhibition was dependent on CD23 binding and the phosphorylation of extracellular signal-related kinase (ERK), and it was mediated via suppression of interleukin-4-induced STAT6 phosphorylation. Treatment with PD98059, a specific inhibitor of mitogen-activated protein kinase kinase 1 (MAPKK1 (MEK1)) and MEK2 reversed the ability of GE2 to decrease CSR and STAT6 phosphorylation. GE2 stimulation induced ERK phosphorylation, whereas it did not alter the phosphorylation of c-Jun N-terminal kinase or p38 MAPK. The ability of GE2 to block human isotype switching to epsilon, in addition to its already demonstrated ability to inhibit mast cell and basophil function, suggests that it will provide an important novel benefit in the treatment of IgE-mediated diseases.

L5 ANSWER 5 OF 5 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 5

2003323238 EMBASE Fc.epsilon.RI-Fc.gamma.RII coaggregation inhibits IL-16 production from human langerhans-like dendritic cells. Kepley C.L.; Zhang K.; Zhu D.; Saxon A.. C.L. Kepley, Department of Internal Medicine, Div. Rheumatology, Allerg./Immunol., P.O. Box 263 MCV Station, Richmond, VA 23298, United States. clkepley@mail1.veu.edu. Clinical Immunology Vol. 108, No. 2, pp. 89-94 1 Aug 2003.

Refs: 28.

ISSN: 1521-6616. CODEN: CLIIFY

Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 20030828

AB Langerhans-like dendritic cells (LLDC) express the high-affinity IgE receptor Fc.epsilon.RI form that lacks the β -chain, and may play an important role in allergic inflammation via production of IL-16. Secretion of mediators by human mast cells and basophils is mediated through Fc.epsilon.RI and is decreased by coaggregating these receptors to the low-affinity IgG receptor, Fc.gamma.RII. We used a recently described human Ig fusion protein (GE2), which is composed of key portions of the human γ 1 and the human ϵ heavy chains, to investigate its ability to inhibit IL-16 production from Fc.epsilon.RI-positive Langerhans-like dendritic cells through coaggregation of Fc.gamma.RII and Fc ϵ RI. Unstimulated LLDC-derived from CD14-positive monocytes from atopic donors were shown to express Fc.gamma.RII, an ITIM-containing receptor, but not Fc.epsilon.RI or Fc γ RIII which are activating (ITAM) receptors. When passively sensitized with antigen-specific, human IgE and then challenged with antigen, LLDC were stimulated to produce IL-16. However, when Fc ϵ RI and Fc.gamma.RII were coaggregated with GE2, IL-16 production was significantly inhibited. Exposure of LLDCs to GE2 alone did not induce IL-16 production. Our results further extend our studies demonstrating the ability of GE2 to inhibit Fc.epsilon.RI-mediated responses through coaggregation with Fc.gamma.RIIB and at the same time show that human LDCC can be modulated in a fashion similar to mast cells and basophils. .COPYRGT. 2003 Elsevier Inc. All rights reserved.

=> s human gamma 1 heavy chain fusion
L6 0 HUMAN GAMMA 1 HEAVY CHAIN FUSION

=> s Fc epsilon fusion
L7 12 FC EPSILON FUSION

=> dup remove l7
PROCESSING COMPLETED FOR L7
L8 5 DUP REMOVE L7 (7 DUPLICATES REMOVED)

=> d l8 1-5 chib abs

L8 ANSWER 1 OF 5 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 1

2005333077 EMBASE Novel treatments for food allergy. Pons L.; Burks W.. Dr. W. Burks, Duke University Medical Center, Pediatric Allergy and Immunology Department, Box 3530, Durham, NC 27710, United States. Wesley.Burks@duke.edu. Expert Opinion on Investigational Drugs Vol. 14, No. 7, pp. 829-834 2005.

Refs: 44.

ISSN: 1354-3784. CODEN: EOIDER

Pub. Country: United Kingdom. Language: English. Summary Language: English.

ED Entered STN: 20050825

AB Food allergy is a major cause of life-threatening hypersensitivity

reactions. Currently, the strict avoidance of the allergenic food and ready access to self-injectable adrenaline is the standard of care for food allergy. Based on extensive characterisation of food allergens and a better understanding of the immunological mechanisms underlying allergic disease, promising therapeutic modalities for the treatment and eventual prevention of food allergy are being developed. Novel immunotherapeutic strategies include peptide immunotherapy, traditional Chinese medicine, mutated or homologous protein immunotherapy, DNA immunisation and immunisation with immunostimulatory sequences, which all strive to elicit a decreased T helper cell type 2-like response or tolerance by the immune system in response to a specific food allergen. Other approaches such as the anti-IgE therapy or the Fcγ-Fcε fusion protein aim at preventing the release of mediators by mast cells. It is the combination of these different approaches that would probably offer the best treatment option for food-allergic patients in a not too distant future. .COPYRGT. 2005 Ashley Publications Ltd.

- L8 ANSWER 2 OF 5 MEDLINE on STN DUPLICATE 2
 2005032334. PubMed ID: 15640700. Genetically engineered negative signaling molecules in the immunomodulation of allergic diseases. Saxon Andrew; Zhu Daocheng; Zhang Ke; Allen Lisa Chan; Kepley Christopher L. (The Hart and Louise Lyon Laboratory, Division of Clinical Immunology/Allergy, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095-1680, USA.. asaxon@mednet.ucla.edu) . Current opinion in allergy and clinical immunology, (2004 Dec) Vol. 4, No. 6, pp. 563-8. Ref: 29. Journal code: 100936359. ISSN: 1528-4050. Pub. country: United States. Language: English.
- AB PURPOSE OF REVIEW: This review summarizes current knowledge regarding the control of human mast cell and basophil signaling and recent developments using a new therapeutic platform consisting of a human bifunctional gamma and epsilon heavy chain (Fc gamma-Fc epsilon) protein to inhibit allergic reactivity. RECENT FINDINGS: Crosslinking of Fc gamma RIIb to Fc epsilon RI on human mast cells and basophils by a genetically engineered Fc gamma-Fc epsilon protein (GE2) leads to the inhibition of mediator release upon Fc epsilon RI challenge. GE2 protein was shown to inhibit cord blood-derived mast cell and peripheral blood basophil mediator release in vitro in a dose-dependent fashion, including inhibition of human IgE reactivity to cat. IgE-driven mediator release from lung tissue was also inhibited by GE2. The mechanism of inhibition in mast cells included alterations in IgE-mediated Ca mobilization, spleen tyrosine kinase phosphorylation and the formation of downstream of kinase-growth factor receptor-bound protein 2-SH2 domain-containing inositol 5-phosphatase (dok-grb2-SHIP) complexes. Proallergic effects of Langerhan's like dendritic cells and B-cell IgE switching were also inhibited by GE2. In vivo, GE2 was shown to block passive cutaneous anaphylaxis driven by human IgE in mice expressing the human Fc epsilon RI and inhibit skin test reactivity to dust mite antigen in a dose-dependent manner in rhesus monkeys. SUMMARY: The balance between positive and negative signaling controls mast cell and basophil reactivity, which is critical in the expression of human allergic diseases. This approach using a human Fc gamma-Fc epsilon fusion protein to co-aggregate Fc epsilon RI with the Fc gamma RII holds promise as a new therapeutic platform for the immunomodulation of allergic diseases and potentially other mast cell/basophil-dependent disease states.
- L8 ANSWER 3 OF 5 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 3
 2004360868 EMBASE Inhibition of allergen-specific IgE reactivity by a human Ig Fcγ-Fcε bifunctional fusion protein. Zhang K.; Kepley C.L.; Terada T.; Zhu D.; Perez H.; Saxon A.. Dr. A. Saxon, Div. of Clinical Immunology/Allergy, Department of Medicine, David Geffen Sch. of Med. at UCLA, Los Angeles, CA 90095-1680, United States. asaxon@mednet.ucla.edu. Journal of Allergy and Clinical Immunology Vol. 114, No. 2, pp. 321-327 2004. Refs: 22.

ISSN: 0091-6749. CODEN: JACIBY

S 0091-6749(04)01408-3. Pub. Country: United States. Language: English.

Summary Language: English.

ED Entered STN: 20040909

AB Background Coaggregating FcεRI with FcγRII receptors holds great potential for treatment of IgE-mediated disease by inhibiting FcεRI signaling. We have previously shown that an Fcγ-Fcε fusion protein, human IgG-IgE Fc fusion protein (GE2), could inhibit FcεRI-mediated mediator releases in vitro and in vivo. Objective We sought to test whether GE2 was capable of blocking mediator release from FcεRI cells sensitized with IgE in vivo or in vitro before exposure to GE2, a critical feature for GE2 to be clinically applicable. Methods GE2 was tested for its ability to inhibit Fel d 1-induced mediator release from human blood basophils from subjects with cat allergy, human lung-derived mast cells, human FcεRIα transgenic mice sensitized with human cat allergic serum, and rhesus monkeys naturally allergic to the dust mite Dermatophagoides farinae. Results Basophils from subjects with cat allergy and lung mast cells degranulate when challenged with Fel d 1 and anti-IgE, respectively. GE2 itself did not induce mediator release but strongly blocked this Fel d 1- and anti-IgE-driven mediator release. GE2 was able to block Fel d 1-driven passive cutaneous anaphylaxis at skin sites sensitized with human serum from subjects with cat allergy in human FcεRIα transgenic mice, but by itself, GE2 did not induce a passive cutaneous anaphylaxis reaction. Finally, GE2 markedly inhibited skin test reactivity to D farinae in monkeys naturally allergic to this allergen, with complete inhibition being observed at 125 ng. Conclusion GE2 is able to successfully compete for FcεRs and FcγRs on cells presensitized in vitro and in vivo and lead to inhibition of IgE-mediated reactivity through coaggregation of FcεRI with FcγRII.

L8 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN

2004:109284 Document No. 140:269419 Utilizing Fcε-Bak chimeric protein for studying IgE-FcεRI interactions. Belostotsky, Ruth; Lorberboum-Galski, Haya (Hadassah Medical School, Department of Cellular Biochemistry and Human Genetics, Hebrew University, Jerusalem, 91120, Israel). Clinical Immunology (San Diego, CA, United States), 110(1), 89-99 (English) 2004. CODEN: CLIIFY. ISSN: 1521-6616. Publisher: Elsevier Science.

AB The authors previously constructed a pro-apoptotic Fcε-Bak chimeric protein, targeted against cells expressing the IgE high affinity receptor (FcεRI). The authors demonstrated that the chimeric protein is internalized by target mast cells and kills them. These results, which constitute a promising basis for applying this approach to antiallergic therapy, raise some theoretical questions with respect to two major issues: (a) is the monomeric Fcε-Bak-FcεRI complex able to undergo endocytosis, and (b) does the receptor binding domain of human IgE (Fcε) react with rodent FcεRI. In an attempt to answer these questions, the authors have now thoroughly investigated the interaction of human (h) and mouse (m) Fcε-Bak with FcεRI-pos. cells. Using established cultures of rodent and human origin, as well as a primary mouse mast cell culture, the authors demonstrate that binding of the chimeric protein to the membrane is followed by quick endocytosis, leading to the apoptosis of specific cells. The authors also confirm that this interaction depends on FcεRI and not on other IgE receptors. The authors found that the effect of Fcε-Bak on the cells depends on the level of surface FcεRI expression, but not on the origin of the target cells or of the Fcε moiety. The authors suggest that endocytosis of the monomeric Fcε-Bak-FcεRI complex results from the inability of Fcε-Bak to transduce signals, characteristic of the monomeric IgE-FcεRI complex due to the absence of the variable portion of the IgE mol. The results also indicate that at least the Fcε fragment of human IgE is able to interact with both human and rodent

FcεRI.

L8 ANSWER 5 OF 5 MEDLINE on STN DUPLICATE 4
2002245565. PubMed ID: 11984598. A novel human immunoglobulin Fc gamma Fc epsilon bifunctional fusion protein inhibits Fc epsilon RI-mediated degranulation. Zhu Daocheng; Kepley Christopher L; Zhang Min; Zhang Ke; Saxon Andrew. (The Hart and Louise Lyon Laboratory, Division of Clinical Immunology/Allergy, Department of Medicine, University of California Los Angeles School of Medicine, Los Angeles, California, USA.) Nature medicine, (2002 May) Vol. 8, No. 5, pp. 518-21. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB Human mast cells and basophils that express the high-affinity immunoglobulin E (IgE) receptor, Fc epsilon receptor 1 (Fc epsilon RI), have key roles in allergic diseases. Fc epsilon RI cross-linking stimulates the release of allergic mediators. Mast cells and basophils co-express Fc gamma RIIB, a low affinity receptor containing an immunoreceptor tyrosine-based inhibitory motif and whose co-aggregation with Fc epsilon RI can block Fc epsilon RI-mediated reactivity. Here we designed, expressed and tested the human basophil and mast-cell inhibitory function of a novel chimeric fusion protein, whose structure is gamma Hinge-CH gamma 2-CH gamma 3-15aa linker-CH epsilon 2-CH epsilon 3-CH epsilon 4. This Fc gamma Fc epsilon fusion protein was expressed as the predicted 140-kappa D dimer that reacted with anti-human epsilon- and gamma-chain specific antibodies. Fc gamma Fc epsilon bound to both human Fc epsilon RI and Fc gamma RII. It also showed dose- and time-dependent inhibition of antigen-driven IgE-mediated histamine release from fresh human basophils sensitized with IgE directed against NIP (4-hydroxy-3-iodo-5-nitrophenylacetyl). This was associated with altered Syk signaling. The fusion protein also showed increased inhibition of human anti-NP (4-hydroxy-3-nitrophenylacetyl) and anti-dansyl IgE-mediated passive cutaneous anaphylaxis in transgenic mice expressing human Fc epsilon RI alpha. Our results show that this chimeric protein is able to form complexes with both Fc epsilon RI and Fc gamma RII, and inhibit mast-cell and basophil function. This approach, using a Fc gamma Fc epsilon fusion protein to co-aggregate Fc epsilon RI with a receptor containing an immunoreceptor tyrosine-based inhibition motif, has therapeutic potential in IgE- and Fc epsilon RI-mediated diseases.

=> s Fc gamma fusion

L9 12 FC GAMMA FUSION

=> dup remove l9

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L10 4 DUP REMOVE L9 (8 DUPLICATES REMOVED)

=> d l10 1-4 cbib abs

L10 ANSWER 1 OF 4 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 1
2006081167 EMBASE Expression and transport functionality of FcRn within rat alveolar epithelium: A study in primary cell culture and in the isolated perfused lung. Sakagami M.; Omid Y.; Campbell L.; Kandalaft L.E.; Morris C.J.; Barar J.; Gumbleton M.. M. Gumbleton, Pharmaceutical Cell Biology, Welsh School of Pharmacy, Cardiff University, Cardiff CF10 3XF, United Kingdom. gumbleton@cardiff.ac.uk. Pharmaceutical Research Vol. 23, No. 2, pp. 270-279 2006.
Refs: 40.
ISSN: 0724-8741. E-ISSN: 1573-904X. CODEN: PHREEB
Pub. Country: United States. Language: English. Summary Language: English.
ED Entered STN: 20060310
AB Purpose. The neonatal constant region fragment receptor (FcRn) binds and transports IgG. FcRn expression in the upper tracheobronchial airways of the lung is recognized. In this study, we sought to characterize the

functional expression of FcRn within alveolar regions of lung tissue. Methods. FcRn immunohistochemistry was performed on intact rat lung. FcRn expression [Western blot, reverse transcription-polymerase chain reaction (RT-PCR), and immunofluorescence microscopy] and IgG transport functionality were assessed in an in vitro rat alveolar epithelial primary cell culture model. An isolated perfused rat lung model was used to examine IgG transport across pulmonary epithelium from airspace to perfusate. Results. FcRn is expressed in intact alveolar epithelium, substantiated by expression and functionality in an in vitro alveolar epithelial model within which IgG transport was temperature sensitive, concentration dependent, and inhibited by excess unlabeled IgG and, to a disproportionate level, by anti-FcRn antibody. Saturable IgG transport across pulmonary epithelium was evident in an isolated perfused rat lung, inhibitable by competing IgG, and displayed a relatively low maximal net IgG absorptive rate of approximately 80 ng/h. Conclusion. Pulmonary epithelium expresses functional FcRn providing an absorption pathway potentially important for highly potent Fc γ - fusion proteins but unlikely to be of quantitative significance for the systemic delivery of inhaled therapeutic monoclonal IgGs. .COPYRGT. 2006 Springer Science + Business Media, Inc.

L10 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN

2002:977608 Document No. 138:54553 Fc ϵ - Fc γ

fusion proteins for treatment of allergy and asthma. An, Ling-Ling; Wu, Herren; Fung, Michael S. C. (Tanox, Inc., USA). PCT Int. Appl. WO 2002102320 A2 20021227, 33 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US19448 20020614. PRIORITY: US 2001-2001/PV298710 20010615.

AB The present invention includes Fc ϵ fragments conjugated with Fc γ fragments, for example, Fc ϵ 1-Hinge-Fc ϵ 2-Fc ϵ 3-Fc ϵ 4-Fc γ ; Hinge-Fc ϵ 2-Fc ϵ 3-Fc ϵ 4-Fc γ ; Fc ϵ 2-Fc ϵ 3-Fc ϵ 4-Fc γ ; Fc ϵ 2-Fc ϵ 3-Fc γ ; Fc ϵ 3-Fc γ ; and Fc ϵ 3-Fc ϵ 4-Fc γ , or any derivative or peptide, which has equivalent immunol. function. The Fc γ fragment may be a fragment of any of the IgG subclasses (IgG1, IgG2, IgG3, or IgG4), preferably IgG1 or IgG3, wherein the fragment binds Fc γ RIIB. The present invention also includes compns. suitable for administering to a patient suffering from an allergic disease comprising the fusion protein construct in a pharmaceutical composition including, for example, an excipient, diluant, or carrier. This treatment may be combined with anti-IgE therapy or allergen immunotherapy.

L10 ANSWER 3 OF 4 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 2

2000375319 EMBASE Ectodomain shedding of epidermal growth factor receptor ligands is required for keratinocyte migration in cutaneous wound healing. Tokumaru S.; Higashiyama S.; Endo T.; Nakagawa T.; Miyagawa J.-I.; Yamamori K.; Hanakawa Y.; Ohmoto H.; Yoshino K.; Shirakata Y.; Matsuzawa Y.; Hashimoto K.; Taniguchi N.. Dr. S. Higashiyama, Department of Biochemistry, School of Allied Health Science, Osaka University Faculty of Medicine, 1-7 Yamadaoka, Suita, Osaka 565-0871, Japan. shigeki@sahs.med.osaka-u.ac.jp. Journal of Cell Biology Vol. 151, No. 2, pp. 209-219 16 Oct 2000. Refs: 38.

ISSN: 0021-9525. CODEN: JCLBA3

Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 20001127

AB Keratinocyte proliferation and migration are essential to cutaneous wound healing and are, in part, mediated in an autocrine fashion by epidermal growth factor receptor (EGFR)-ligand interactions. EGFR ligands are initially synthesized as membrane-anchored forms, but can be processed and shed as soluble forms. We provide evidence here that wound stimuli induce keratinocyte shedding of EGFR ligands in vitro, particularly the ligand heparin-binding EGF-like growth factor (HB-EGF). The resulting soluble ligands stimulated transient activation of EGFR. OSU8-1, an inhibitor of EGFR ligand shedding, abrogated the wound-induced activation of EGFR and caused suppression of keratinocyte migration in vitro. Soluble EGFR-immunoglobulin G-Fc fusion protein, which is able to neutralize all EGFR ligands, also suppressed keratinocyte migration in vitro. The application of OSU8-1 to wound sites in mice greatly retarded reepithelialization as the result of a failure in keratinocyte migration, but this effect could be overcome if recombinant soluble HB-EGF was added along with OSU8-1. These findings indicate that the shedding of EGFR ligands represents a critical event in keratinocyte migration, and suggest their possible use as an effective clinical treatment in the early phases of wound healing.

L10 ANSWER 4 OF 4 MEDLINE on STN DUPLICATE 3
 1998180360. PubMed ID: 9521065. Regulation of cytoplasmic, surface and soluble forms of CD40 ligand in mouse B cells. Wykes M; Poudrier J; Lindstedt R; Gray D. (Department of Immunology, Imperial College School of Medicine, Hammersmith Hospital, London, GB.) European journal of immunology, (1998 Feb) Vol. 28, No. 2, pp. 548-59. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB CD40 and CD40 ligand (CD40L) form one of most important receptor-ligand pairs that dock during T-B cell interactions as part of T-dependent antibody responses. It has been reported that among other cell types, B cells can express CD40L. Here we show that a large proportion of mouse B cells express CD40L in their cytoplasm, but not on the surface and that this is readily released as a soluble molecule. Thus, in their resting state up to 50% of mouse B cells express CD40L within their cytoplasm and both the proportion of cells expressing and the amount of CD40L is increased by signaling through immunoglobulin (Ig) or CD38. In contrast, T cell-derived signals such as CD40L (anti-CD40) or Th2-type cytokines cause a decrease in CD40L expression that is related to a release of a soluble form of the molecule from the cell. Supernatants from B cells activated with anti-Ig and anti-CD40 contain CD40L in a variety of forms (18 kDa, 33 kDa and 66 kDa) that are readily detectable by immunoprecipitation with CD40-Fc gamma fusion protein (CD40-Ig) followed by Western blotting with anti-CD40L antibody (MR1). The 33-kDa species is distinct from the 39-kDa membrane-bound molecule found in activated T cells or in resting B cells and appears to be a novel soluble form of CD40L. Inhibition of T cell-independent in vitro stimulation of B cells with CD40-Ig or anti-CD40L suggests that the B cell-derived soluble CD40L or CD40L expressed on the B cell surface can play a positive role in B cell proliferation.

=> s (saxon a?/au or zhang k?/au or zhu d?/au)
 L11 21031 (SAXON A?/AU OR ZHANG K?/AU OR ZHU D?/AU)

=> s l11 and Fc epsilon
 L12 76 L11 AND FC EPSILON

=> s l12 and fusion
 L13 27 L12 AND FUSION

=> dup remove l13
 PROCESSING COMPLETED FOR L13
 L14 9 DUP REMOVE L13 (18 DUPLICATES REMOVED)

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L14 ANSWER 1 OF 9 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 1

2005187007 EMBASE A chimeric human-cat fusion protein blocks cat-induced allergy. Zhu D.; Kepley C.L.; Zhang K.; Terada T.; Yamada T.; Saxon A.. D. Zhu, Hart and Louise Lyon Laboratory, Department of Medicine, UCLA School of Medicine, 10833 Le Conte Avenue, Los Angeles, CA 90095-1680, United States. dczhu@ucla.edu. Nature Medicine Vol. 11, No. 4, pp. 446-449 2005.

Refs: 28.

ISSN: 1078-8956. CODEN: NAMEFI

Pub. Country: United Kingdom. Language: English. Summary Language: English.

ED Entered STN: 20050602

AB Animal allergens are an important cause of asthma and allergic rhinitis. We designed and tested a chimeric human-cat fusion protein composed of a truncated human IgG Fc γ 1 and the major cat allergen Fel d1, as a proof of concept for a new approach to allergy immunotherapy. This Fc γ -Fel d1 protein induced dose-dependent inhibition of Fel d1-driven IgE-mediated histamine release from cat-allergic donors' basophils and sensitized human cord blood-derived mast cells. Such inhibition was associated with altered Syk and ERK signaling. The Fc γ -Fel d1 protein also blocked in vivo reactivity in Fc ϵ 1 transgenic mice passively sensitized with human IgE antibody to cat and in Balb/c mice actively sensitized against Fel d1. The Fc γ -Fel d1 protein alone did not induce mediator release. Chimeric human Fc γ -allergen fusion proteins may provide a new therapeutic platform for the immune-based therapy of allergic disease.

L14 ANSWER 2 OF 9 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 2

2004357862 EMBASE Co-aggregation of Fc γ RII with Fc ϵ 1 on human mast cells inhibits antigen-induced secretion and involves SHIP-Grb2-Dok complexes. Kepley C.L.; Taghavi S.; Mackay G.; Zhu D.; Morel P.A.; Zhang K.; Ryan J.J.; Satin L.S.; Zhang M.; Pandolfi P.P.; Saxon A.. C.L. Kepley, Dept. of Internal Medicine, Div. of Rheumatol., Allerg./Immunol., MCV Station, P. O. Box 263, Richmond, VA 23298, United States. clkepley@mail1.vcu.edu. Journal of Biological Chemistry Vol. 279, No. 34, pp. 35139-35149 20 Aug 2004.

Refs: 64.

ISSN: 0021-9258. CODEN: JBCHA3

Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 20040916

AB Signaling through the high affinity IgE receptor Fc ϵ 1 on human basophils and rodent mast cells is decreased by co-aggregating these receptors to the low affinity IgG receptor Fc γ RII. We used a recently described fusion protein, GE2, which is composed of key portions of the human γ 1 and the human ϵ heavy chains, to dissect the mechanisms that lead to human mast cell and basophil inhibition through co-aggregation of Fc γ RII and Fc ϵ 1. Unstimulated human mast cells derived from umbilical cord blood express the immunoreceptor tyrosine-based inhibitory motif-containing receptor Fc γ RII but not Fc γ RI or Fc γ RIII. Interaction of the mast cells with GE2 alone did not cause degranulation. Co-aggregating Fc ϵ 1 and Fc γ RII with GE2 1) significantly inhibited IgE-mediated histamine release, cytokine production, and Ca(2+) mobilization, 2) reduced the antigen-induced morphological changes associated with mast cell degranulation, 3) reduced the tyrosine phosphorylation of several cellular substrates, and 4) increased the tyrosine phosphorylation of the adapter protein downstream of kinase 1 (p62(dok); Dok), growth factor receptor-bound protein 2 (Grb2), and SH2 domain containing inositol 5-phosphatase (SHIP). Tyrosine phosphorylation of Dok was associated with

increased binding to Grb2. Surprisingly, in non-stimulated cells, there were complexes of phosphorylated SHIP-Grb2-Dok that were lost upon IgE receptor activation but retained under conditions of **Fc**.

epsilon-Fc co-aggregation. Finally, studies using mast cells from Dok-1 knock-out mice showed that IgE alone triggers degranulation supporting an inhibitory role for Dok degranulation. Our results demonstrate how human **Fce** RI-mediated responses can be inhibited by co-aggregation with FcγRIIB and implicate Dok, SHIP, and Grb2 as key intermediates in regulating antigen-induced mediator release.

L14 ANSWER 3 OF 9 MEDLINE on STN DUPLICATE 3
2005032334. PubMed ID: 15640700. Genetically engineered negative signaling molecules in the immunomodulation of allergic diseases. **Saxon Andrew; Zhu Daocheng; Zhang Ke**; Allen Lisa Chan; Kepley Christopher L. (The Hart and Louise Lyon Laboratory, Division of Clinical Immunology/Allergy, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095-1680, USA.. asaxon@mednet.ucla.edu) . Current opinion in allergy and clinical immunology, (2004 Dec) Vol. 4, No. 6, pp. 563-8. Ref: 29. Journal code: 100936359. ISSN: 1528-4050. Pub. country: United States. Language: English.

AB PURPOSE OF REVIEW: This review summarizes current knowledge regarding the control of human mast cell and basophil signaling and recent developments using a new therapeutic platform consisting of a human bifunctional gamma and epsilon heavy chain (Fc gamma-Fc **epsilon**) protein to inhibit allergic reactivity. RECENT FINDINGS: Crosslinking of Fc gamma RIIB to **Fc epsilon** RI on human mast cells and basophils by a genetically engineered Fc gamma-Fc **epsilon** protein (GE2) leads to the inhibition of mediator release upon **Fc epsilon** RI challenge. GE2 protein was shown to inhibit cord blood-derived mast cell and peripheral blood basophil mediator release in vitro in a dose-dependent fashion, including inhibition of human IgE reactivity to cat. IgE-driven mediator release from lung tissue was also inhibited by GE2. The mechanism of inhibition in mast cells included alterations in IgE-mediated Ca mobilization, spleen tyrosine kinase phosphorylation and the formation of downstream of kinase-growth factor receptor-bound protein 2-SH2 domain-containing inositol 5-phosphatase (dok-grb2-SHIP) complexes. Proallergic effects of Langerhan's like dendritic cells and B-cell IgE switching were also inhibited by GE2. In vivo, GE2 was shown to block passive cutaneous anaphylaxis driven by human IgE in mice expressing the human **Fc epsilon** RI and inhibit skin test reactivity to dust mite antigen in a dose-dependent manner in rhesus monkeys. SUMMARY: The balance between positive and negative signaling controls mast cell and basophil reactivity, which is critical in the expression of human allergic diseases. This approach using a human Fc gamma-Fc **epsilon** fusion protein to co-aggregate **Fc epsilon** RI with the Fc gamma RII holds promise as a new therapeutic platform for the immunomodulation of allergic diseases and potentially other mast cell/basophil-dependent disease states.

L14 ANSWER 4 OF 9 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 4
2004360868 EMBASE Inhibition of allergen-specific IgE reactivity by a human Ig Fcγ- **Fce** bifunctional fusion protein. **Zhang K.**; Kepley C.L.; Terada T.; **Zhu D.**; Perez H.; **Saxon A.** Dr. A. Saxon, Div. of Clinical Immunology/Allergy, Department of Medicine, David Geffen Sch. of Med. at UCLA, Los Angeles, CA 90095-1680, United States. asaxon@mednet.ucla.edu. Journal of Allergy and Clinical Immunology Vol. 114, No. 2, pp. 321-327 2004.
Refs: 22.
ISSN: 0091-6749. CODEN: JACIBY
S 0091-6749(04)01408-3. Pub. Country: United States. Language: English.

Summary Language: English.

ED Entered STN: 20040909

AB Background Coaggregating **Fcε** RI with **Fcγ**RII receptors holds great potential for treatment of IgE-mediated disease by inhibiting **Fcε** RI signaling. We have previously shown that an **Fcγ**- **Fcε** fusion protein, human IgG-IgE **Fc** fusion protein (GE2), could inhibit **Fcε** RI-mediated mediator releases in vitro and in vivo. Objective We sought to test whether GE2 was capable of blocking mediator release from **Fcε** RI cells sensitized with IgE in vivo or in vitro before exposure to GE2, a critical feature for GE2 to be clinically applicable. Methods GE2 was tested for its ability to inhibit **Fel** d 1-induced mediator release from human blood basophils from subjects with cat allergy, human lung-derived mast cells, human **Fcε** RIα transgenic mice sensitized with human cat allergic serum, and rhesus monkeys naturally allergic to the dust mite *Dermatophagoides farinae*. Results Basophils from subjects with cat allergy and lung mast cells degranulate when challenged with **Fel** d 1 and anti-IgE, respectively. GE2 itself did not induce mediator release but strongly blocked this **Fel** d 1- and anti-IgE-driven mediator release. GE2 was able to block **Fel** d 1-driven passive cutaneous anaphylaxis at skin sites sensitized with human serum from subjects with cat allergy in human **Fcε** RIα transgenic mice, but by itself, GE2 did not induce a passive cutaneous anaphylaxis reaction. Finally, GE2 markedly inhibited skin test reactivity to *D. farinae* in monkeys naturally allergic to this allergen, with complete inhibition being observed at 125 ng. Conclusion GE2 is able to successfully compete for **Fcε** Rs and **Fcγ**Rs on cells presensitized in vitro and in vivo and lead to inhibition of IgE-mediated reactivity through coaggregation of **Fcε** RI with **Fcγ**RII.

L14 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
2003:260853 Document No. 138:285999 Chimeric proteins comprising ITIM motif, antigen and **Fcε** R binding peptide for treating immune diseases. Saxon, Andrew (USA). U.S. Pat. Appl. Publ. US 2003064063 A1 20030403, 51 pp., Cont.-in-part of U.S. Ser. No. 847,208. (English). CODEN: USXXCO. APPLICATION: US 2001-439 20011024. PRIORITY: US 2001-2001/847208 20010501.

AB The invention concerns bifunctional fusion mols., and novel, safer and more efficacious methods for the treatment of immune disorders resulting from excessive or unwanted immune responses. The invention provides methods for the suppression of type I hypersensitive (i.e., IgE-mediated) allergic conditions, methods for the prevention of anaphylactic responses that occur as a result of traditional peptide immunotherapies for allergic and autoimmune disorders, and provides novel methods for the treatment of autoimmune conditions, where the methods have reduced risk of triggering an anaphylactic response. The invention provides novel therapeutic approaches for the treatment of allergic responses, including the prevention of anaphylactic response that can occur from environmental allergen exposure. The invention also provides methods for the treatment of autoimmune disorders such as multiple sclerosis, autoimmune type I diabetes mellitus, and rheumatoid arthritis. The invention also provides methods for preventing anaphylactic response during traditional antigen therapies.

L14 ANSWER 6 OF 9 MEDLINE on STN DUPLICATE 5
2003414071. PubMed ID: 12801927. Inhibition of interleukin-4-induced class switch recombination by a human immunoglobulin **Fc** gamma-**Fcε** chimeric protein. Yamada Takechiyo; Zhu Daocheng; Zhang Ke; Saxon Andrew. (Hart and Louis Laboratory, Division of Clinical Immunology, Department of Medicine, UCLA School of Medicine, California 90095-1680, USA.. ymdtkcy@fmsrsa.fukui-med.ac.jp) . The Journal of biological chemistry, (2003 Aug 29) Vol. 278, No. 35, pp. 32818-24. Electronic Publication: 2003-06-11. Journal code: 2985121R.

ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Immunoglobulin E (IgE) is important in mediating human allergic diseases. We tested the hypothesis that a human Ig Fc gamma-Fc epsilon bifunctional chimeric protein, GE2, would inhibit IgE class switch recombination (CSR) by co-aggregating B-cell CD32 and CD23. Indeed, GE2 directly inhibited epsilon germ-line transcription, subsequent CSR to epsilon and IgE protein production. This CSR inhibition was dependent on CD23 binding and the phosphorylation of extracellular signal-related kinase (ERK), and it was mediated via suppression of interleukin-4-induced STAT6 phosphorylation. Treatment with PD98059, a specific inhibitor of mitogen-activated protein kinase kinase 1 (MAPKK1 (MEK1)) and MEK2 reversed the ability of GE2 to decrease CSR and STAT6 phosphorylation. GE2 stimulation induced ERK phosphorylation, whereas it did not alter the phosphorylation of c-Jun N-terminal kinase or p38 MAPK. The ability of GE2 to block human isotype switching to epsilon, in addition to its already demonstrated ability to inhibit mast cell and basophil function, suggests that it will provide an important novel benefit in the treatment of IgE-mediated diseases.

L14 ANSWER 7 OF 9 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 6

2003323238 EMBASE Fcε RI-FcγRII coaggregation inhibits IL-16 production from human langerhans-like dendritic cells. Kepley C.L.; Zhang K.; Zhu D.; Saxon A.. C.L. Kepley, Department of Internal Medicine, Div. Rheumatology, Allerg./Immunol., P.O. Box 263 MCV Station, Richmond, VA 23298, United States. clkepley@mail1.veu.edu. Clinical Immunology Vol. 108, No. 2, pp. 89-94 1 Aug 2003. Refs: 28.

ISSN: 1521-6616. CODEN: CLIIFY

Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 20030828

AB Langerhans-like dendritic cells (LLDC) express the high-affinity IgE receptor Fcε RI form that lacks the β-chain, and may play an important role in allergic inflammation via production of IL-16. Secretion of mediators by human mast cells and basophils is mediated through Fcε RI and is decreased by coaggregating these receptors to the low-affinity IgG receptor, FcγRII. We used a recently described human Ig fusion protein (GE2), which is composed of key portions of the human γ1 and the human ε heavy chains, to investigate its ability to inhibit IL-16 production from Fc.εpsilon .RI-positive Langerhans-like dendritic cells through coaggregation of FcγRII and Fcε RI. Unstimulated LLDC-derived from CD14-positive monocytes from atopic donors were shown to express FcγRII, an ITIM-containing receptor, but not Fc.εpsilon .RI or FcγRIII which are activating (ITAM) receptors. When passively sensitized with antigen-specific, human IgE and then challenged with antigen, LLDC were stimulated to produce IL-16. However, when Fcε RI and FcγRII were coaggregated with GE2, IL-16 production was significantly inhibited. Exposure of LLDCs to GE2 alone did not induce IL-16 production. Our results further extend our studies demonstrating the ability of GE2 to inhibit Fc.εpsilon .RI-mediated responses through coaggregation with FcγRIIB and at the same time show that human LDCC can be modulated in a fashion similar to mast cells and basophils. .COPYRGT. 2003 Elsevier Inc. All rights reserved.

L14 ANSWER 8 OF 9 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN 2004:72749 Document No.: PREV200400071901. SHIP-Grb2-Dok complexes prevent

Fc(εpsilon)RI-mediated human mast cell activation and regulate Fc(gamma)RII-mediated inhibition. Kepley, Christopher Lynn [Reprint Author]; Mackay, Graham; Morel, Penelope A.; Zhu, Daocheng; Ke, Zhang; Saxon, Andrew. Internal Medicine, Medical College of Virginia, Virginia Commonwealth University, 1112 E Clay

St, McGuire Hall Room 4-115B, Richmond, VA, 23298, USA. FASEB Journal, (April 14 2003) Vol. 17, No. 7, pp. C15. print.
Meeting Info.: 90th Anniversary Annual Meeting of the American Association of Immunologists. Denver, CO, USA. May 06-10, 2003. American Association of Immunologists.
ISSN: 0892-6638 (ISSN print). Language: English.

L14 ANSWER 9 OF 9 MEDLINE on STN DUPLICATE 7
2002245565. PubMed ID: 11984598. A novel human immunoglobulin Fc gamma Fc epsilon bifunctional fusion protein inhibits Fc epsilon RI-mediated degranulation.
Zhu Daocheng; Kepley Christopher L; Zhang Min; Zhang Ke; Saxon Andrew. (The Hart and Louise Lyon Laboratory, Division of Clinical Immunology/Allergy, Department of Medicine, University of California Los Angeles School of Medicine, Los Angeles, California, USA.) Nature medicine, (2002 May) Vol. 8, No. 5, pp. 518-21. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.
AB Human mast cells and basophils that express the high-affinity immunoglobulin E (IgE) receptor, Fc epsilon receptor 1 (Fc epsilon RI), have key roles in allergic diseases. Fc epsilon RI cross-linking stimulates the release of allergic mediators. Mast cells and basophils co-express Fc gamma RIIB, a low affinity receptor containing an immunoreceptor tyrosine-based inhibitory motif and whose co-aggregation with Fc epsilon RI can block Fc epsilon RI-mediated reactivity. Here we designed, expressed and tested the human basophil and mast-cell inhibitory function of a novel chimeric fusion protein, whose structure is gamma Hinge-CH gamma 2-CH gamma 3-15aa linker-CH epsilon 2-CH epsilon 3-CH epsilon 4. This Fc gamma Fc epsilon fusion protein was expressed as the predicted 140-kappa D dimer that reacted with anti-human epsilon- and gamma-chain specific antibodies. Fc gamma Fc epsilon bound to both human Fc epsilon RI and Fc gamma RII. It also showed dose- and time-dependent inhibition of antigen-driven IgE-mediated histamine release from fresh human basophils sensitized with IgE directed against NIP (4-hydroxy-3-iodo-5-nitrophenylacetyl). This was associated with altered Syk signaling. The fusion protein also showed increased inhibition of human anti-NP (4-hydroxy-3-nitrophenylacetyl) and anti-dansyl IgE-mediated passive cutaneous anaphylaxis in transgenic mice expressing human Fc epsilon RI alpha. Our results show that this chimeric protein is able to form complexes with both Fc epsilon RI and Fc gamma RII, and inhibit mast-cell and basophil function. This approach, using a Fc gamma Fc epsilon fusion protein to co-aggregate Fc epsilon RI with a receptor containing an immunoreceptor tyrosine-based inhibition motif, has therapeutic potential in IgE- and Fc epsilon RI-mediated diseases.

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L15 19 L11 AND IGE FC

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L16 9 L15 AND FUSION

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L17 5 DUP REMOVE L16 (4 DUPLICATES REMOVED)

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L17 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
2004:679170 Document No. 141:241999 Co-aggregation of FcγRII with FcεRI on Human Mast Cells Inhibits Antigen-induced Secretion and Involves SHIP-Grb2-Dok Complexes. Kepley, Christopher L.; Taghavi,

Sharven; Mackay, Graham; Zhu, Daocheng; Morel, Penelope A.; Zhang, Ke; Ryan, John J.; Satin, Leslie S.; Zhang, Min; Pandolfi, Pier P.; Saxon, Andrew (Department of Internal Medicine, Virginia Commonwealth University Health Systems, Richmond, VA, 23298, USA). Journal of Biological Chemistry, 279(34), 35139-35149 (English) 2004. CODEN: JBCHA3. ISSN: 0021-9258. Publisher: American Society for Biochemistry and Molecular Biology.

- AB Signaling through the high affinity IgE receptor FcεRI on human basophils and rodent mast cells is decreased by co-aggregating these receptors to the low affinity IgG receptor FcγRII. The authors used a recently described **fusion** protein, GE2, which is composed of key portions of the human γ1 and the human ε heavy chains, to dissect the mechanisms that lead to human mast cell and basophil inhibition through co-aggregation of FcγRII and FcεRI. Unstimulated human mast cells derived from umbilical cord blood express the immunoreceptor tyrosine-based inhibitory motif-containing receptor FcγRII but not FcγRI or FcγRIII. Interaction of the mast cells with GE2 alone did not cause degranulation. Co-aggregating FcεRI and FcγRII with GE2 (1) significantly inhibited IgE-mediated histamine release, cytokine production, and Ca²⁺ mobilization, (2) reduced the antigen-induced morphol. changes associated with mast cell degranulation, (3) reduced the tyrosine phosphorylation of several cellular substrates, and (4) increased the tyrosine phosphorylation of the adapter protein downstream of kinase 1 (p62dok; Dok), growth factor receptor-bound protein 2 (Grb2), and SH2 domain containing inositol 5-phosphatase (SHIP). Tyrosine phosphorylation of Dok was associated with increased binding to Grb2. Surprisingly, in non-stimulated cells, there were complexes of phosphorylated SHIP-Grb2-Dok that were lost upon IgE receptor activation but retained under conditions of Fcε-Fcγ co-aggregation. Finally, studies using mast cells from Dok-1 knock-out mice showed that IgE alone triggers degranulation supporting an inhibitory role for Dok degranulation. The authors' results demonstrate how human FcεRI-mediated responses can be inhibited by co-aggregation with FcγRIIB and implicate Dok, SHIP, and Grb2 as key intermediates in regulating antigen-induced mediator release.

L17 ANSWER 2 OF 5 MEDLINE on STN DUPLICATE 1
2004433011. PubMed ID: 15316510. Inhibition of allergen-specific IgE reactivity by a human Ig Fcγ-Fcε bifunctional **fusion** protein. Zhang Ke; Kepley Christopher L; Terada Tetsuya; Zhu Daocheng; Perez Hector; Saxon Andrew. (Hart and Louis Lyon Laboratory, Division of Clinical Immunology and Allergy, Department of Medicine, University of California Los Angeles School of Medicine, CA 90095-1680, USA.) The Journal of allergy and clinical immunology, (2004 Aug) Vol. 114, No. 2, pp. 321-7. Journal code: 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

- AB BACKGROUND: Coaggregating FcεRI with FcγRII receptors holds great potential for treatment of IgE-mediated disease by inhibiting FcεRI signaling. We have previously shown that an Fcγ-Fcε **fusion** protein, human IgG-IgE Fc **fusion** protein (GE2), could inhibit FcεRI-mediated mediator releases in vitro and in vivo. OBJECTIVE: We sought to test whether GE2 was capable of blocking mediator release from FcεRI cells sensitized with IgE in vivo or in vitro before exposure to GE2, a critical feature for GE2 to be clinically applicable. METHODS: GE2 was tested for its ability to inhibit Fel d 1-induced mediator release from human blood basophils from subjects with cat allergy, human lung-derived mast cells, human FcεRIα transgenic mice sensitized with human cat allergic serum, and rhesus monkeys naturally allergic to the dust mite Dermatophagoides farinae. RESULTS: Basophils from subjects with cat allergy and lung mast cells degranulate when challenged with Fel d 1 and anti-IgE, respectively. GE2 itself did not induce mediator release but strongly blocked this Fel d 1- and anti-IgE-driven mediator release. GE2 was able to block Fel d 1-driven passive cutaneous anaphylaxis at skin sites sensitized with human serum from subjects with cat allergy in human

FcepsilonRIalpha transgenic mice, but by itself, GE2 did not induce a passive cutaneous anaphylaxis reaction. Finally, GE2 markedly inhibited skin test reactivity to D farinae in monkeys naturally allergic to this allergen, with complete inhibition being observed at 125 ng. CONCLUSION: GE2 is able to successfully compete for FcepsilonRs and FcgammaRs on cells presensitized in vitro and in vivo and lead to inhibition of IgE-mediated reactivity through coaggregation of FcepsilonRI with FcgammaRII.

L17 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN

2003:260853 Document No. 138:285999 Chimeric proteins comprising ITIM motif, antigen and FcεR binding peptide for treating immune diseases. **Saxon, Andrew** (USA). U.S. Pat. Appl. Publ. US 2003064063 A1 20030403, 51 pp., Cont.-in-part of U.S. Ser. No. 847,208. (English). CODEN: USXXCO. APPLICATION: US 2001-439 20011024. PRIORITY: US 2001-2001/847208 20010501.

AB The invention concerns bifunctional **fusion** mols., and novel, safer and more efficacious methods for the treatment of immune disorders resulting from excessive or unwanted immune responses. The invention provides methods for the suppression of type I hypersensitive (i.e., IgE-mediated) allergic conditions, methods for the prevention of anaphylactic responses that occur as a result of traditional peptide immunotherapies for allergic and autoimmune disorders, and provides novel methods for the treatment of autoimmune conditions, where the methods have reduced risk of triggering an anaphylactic response. The invention provides novel therapeutic approaches for the treatment of allergic responses, including the prevention of anaphylactic response that can occur from environmental allergen exposure. The invention also provides methods for the treatment of autoimmune disorders such as multiple sclerosis, autoimmune type I diabetes mellitus, and rheumatoid arthritis. The invention also provides methods for preventing anaphylactic response during traditional antigen therapies.

L17 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN

2003:621944 Document No. 139:291008 FcεRI-FcγRII Coaggregation inhibits IL-16 production from human Langerhans-like dendritic cells. **Kepley, Christopher L.; Zhang, Ke; Zhu, Daocheng; Saxon, Andrew** (Medical College of Virginia, Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA, USA). Clinical Immunology (San Diego, CA, United States), 108(2), 89-94 (English) 2003. CODEN: CLIFY. ISSN: 1521-6616. Publisher: Elsevier Science.

AB Langerhans-like dendritic cells (LLDC) express the high-affinity IgE receptor FcεRI form that lacks the β-chain, and may play an important role in allergic inflammation via production of IL-16. Secretion of mediators by human mast cells and basophils is mediated via FcεRI and is decreased by coaggregating these receptors to the low-affinity IgG receptor, FcγRII. The authors used a recently described human Ig **fusion** protein (GE2), which is composed of key portions of the human γ1 and the human ε heavy chains, to investigate its ability to inhibit IL-16 production from FcεRI-pos. Langerhans-like dendritic cells through coaggregation of FcγRII and FcεRI. Unstimulated LLDC-derived from CD14-pos. monocytes from atopic donors were shown to express FcγRII, an ITIM-containing receptor, but not FcεRI or FcγRIII which are activating (ITAM) receptors. When passively sensitized with antigen-specific, human IgE and then challenged with antigen, LLDC were stimulated to produce IL-16. However, when FcεRI and FcγRII were coaggregated with GE2, IL-16 production was inhibited. Exposure of LLDCs to GE2 alone did not induce IL-16 production. The authors' results further extend their studies demonstrating the ability of GE2 to inhibit FcεRI-mediated responses via coaggregation with FcγRIIB and at the same time show that human LDCC can be modulated in a fashion similar to mast cells and basophils.

L17 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN

2002:849789 Document No. 137:368556 Chimeric proteins comprising IgG inhibitory receptor-binding epitope and IgE receptor-binding epitope for

treating allergies and other immune diseases. **Saxon, Andrew; Zhang, Ke; Zhu, Daocheng** (Regents of the University of California, USA). PCT Int. Appl. WO 2002088317 A2 20021107, 116 pp.
 DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US13527 20020501. PRIORITY: US 2001-2001/847208 20010501; US 2001-2001/439 20011024.

AB The invention concerns bifunctional **fusion** mols., and novel, safer and more efficacious methods for the treatment of immune disorders resulting from excessive or unwanted immune responses. The invention provides methods for the suppression of type I hypersensitive (i.e., IgE-mediated) allergic conditions, methods for the prevention of anaphylactic responses that occur as a result of traditional peptide immunotherapies for allergic and autoimmune disorders, and provides novel methods for the treatment of autoimmune conditions, where the methods have reduced risk of triggering an anaphylactic response. The invention provides novel therapeutic approaches for the treatment of allergic responses, including the prevention of anaphylactic response that can occur from environmental allergen exposure. The invention also provides methods for the treatment of autoimmune disorders such as multiple sclerosis, autoimmune type I diabetes mellitus, and rheumatoid arthritis. The invention also provides methods for preventing anaphylactic response during traditional antigen therapies.

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